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08/978,636

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ELAZAR RABBBANI

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EXAMINER

BOWMAN, AMY HUDSON

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

08/978,636

Applicant(s)

RABBBANI ET AL.

Examiner

AMY BOWMAN

Art Unit

1635

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 245,247-255,262,265 and 268-271 is/are pending in the application.
- 4a) Of the above claim(s) 268 and 269 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 245,247-255,262,265, 270, and 271 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 November 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/22/09</u> .  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

Applicant's response filed 12/22/09 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/22/09 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 245, 247-255, 262, 265, and 268-271 are pending in the instant application.

This application contains claims 268 and 269 that are drawn to an invention nonelected with traverse in the reply filed on 10/9/07 and are therefore withdrawn.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/09 has been entered.

Applicant's arguments and/or amendments to the claims filed on 12/22/09 have been fully considered and are persuasive with regards to the rejection under 35 USC 112, 2<sup>nd</sup> paragraph and written description. Therefore, these rejections have been

withdrawn. However, the following rejections are pending and a new grounds of rejection is set forth below.

***Response to Applicants Arguments-- 35 USC § 112***

Claims 245, 247-255, 262, 265, 270, and 271 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This rejection is repeated for the same reasons of record as set forth in the actions mailed 5/31/05, 6/27/06, 4/4/07, 12/26/07, 9/15/08, and 6/22/09.

Although applicant asserts that there is sufficient description for choosing intron sequences, there is not sufficient description for choosing intron sequences within the context of the instant invention, as it is not evident that insertion of any intron into any sequence encoding any intron, especially wherein the insertion is at any position, would result in the instantly recited outcomes. The instant claims are not closed to introns with any specific structural characteristic that would narrow the genus to those introns that are predictably spliced in eukaryotes, as discussed above.

Applicant asserts that methods are well known in the art for introducing artificial introns. It is not disputed that methods are known in the art to introduce artificial introns. However, it is the unpredictable nature of introducing any intron into any nucleic acid sequence at any position that encodes any polymerase with a resultant incapability of the polymerase being expressed in any prokaryotic cell, whereas more than one copy of a nucleic acid sequence is produced when introduced into any

eukaryotic cell. Furthermore, the claims recite that the gene product or protein expressed would be toxic specifically to a prokaryotic cell in the absence of the intron.

Although applicant asserts that that rejection is solely based upon the teachings of Balvay, the rejection is based upon the unpredictability of the instantly claimed extremely large genus of constructs.

Applicants specifically claim that the inserted and inactivating intronic sequences will be spliced out, a process the specification indicates will be carried out by the cellular machinery that normally operates to splice introns out of pre-mRNA sequences. Applicants indicate that such splicing restores native activity to previously inactive proteins. However, the specification as filed does not provide any nucleic acid constructs for which this has actually been shown to demonstrate the predictability of such a broad mechanism. Applicant's specification does not provide sufficient guidance or examples that would enable a skilled artisan to make the disclosed nucleic acid constructs containing sequences that are spliced out by cellular machinery without undue experimentation. Although the specification prophetically considers and discloses making and using such constructs, such a disclosure would not be considered enabling since introducing intervening sequences into nucleic acids alters their secondary structure, which makes their ability to be cleaved by the splicing machinery unpredictable. The specification has not resolved such issues, since no exemplified constructs that contain intervening sequences and are inactive therefore, and by which later processing inside the cell restores activity. Applicants have simply

not shown that such intervening sequences can be spliced out to restore any activity to previously inactive polymerases (or any toxic protein for that matter).

Applicant points to Schwartz, Mayeda and Oshima for teachings of instances where introns have been inserted and spliced in eukaryotic cells and not in prokaryotic cells. It is acknowledged that insertion of an intron into a coding sequence may result in splicing of the sequence in eukaryotic cells. However, applicant is not enabled for inserting any intron into a sequence encoding any polymerase or any gene product with a predictable effect of capability of producing more than one copy of a sequence in a eukaryotic cell while being incapable of being expressed in a prokaryotic cell. The results of Mayeda and Oshima are not enabling for a method of inserting any intron into any polymerase or gene product with the instantly recited outcomes. Mayeda and Oshima teach that determinants essential for splicing is localized in the intron itself plus 3 nt of the 5' exon rather than the overall structure of the pre-mRNA. This does not mean that the structure of the pre-mRNA is not important to the slicing process, just that the 3 nt of the 5' exon were more essential. Furthermore, Mayeda and Oshima are considered evidence that determinants/structure of the intron itself is crucial to the process, this supporting that not necessarily any intron would result in the instant outcomes when inserted into a nucleic acid encoding any gene product or polymerase. Furthermore, the 3 nt of the 5' exon were crucial for splicing, wherein instant claim 245, for example, embraces insertion anywhere in any sequence encoding any polymerase with the instantly recited outcomes. Although applicant argues that intron sequences inserted into a target gene at (C/A) AGG sites are likely

to be spliced out, instant claim 245, for example, does not require this. Furthermore, Balvay et al. is evidence that the target structure does in fact play a role in splicing, as discussed above.

Applicant points to a statement of Balvay et al. "It is important to stress that in the absence of *in vivo* experiments or *in vitro* systems where transcription and splicing are coupled, all these conclusions about the functional significance of secondary structure should be taken as tentative ones." Although applicant interprets this statement as a tentative conclusion that is contrary to practical exercises that have been carried out generating *in vivo* data that introduction of introns into selected sites is a predictable art with a high likelihood of success, the statement of Balvay et al. actually supports the examiner's position. It is agreed that the issues of unpredictability due to secondary structure as taught by Balvay et al. could be overcome by *in vivo* experimentation, Balvay et al. is evidence that there are additional considerations such as secondary structure that would lead to unpredictability, absence evidence to the contrary. The instantly recited constructs have extremely broad structural characteristics that were not enabled by the instant specification or the state of the art at the time of filing. Although applicant asserts that Balvay is directed to special occasions, a conclusion of lack of enablement means that, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

Although applicant argues that Balvay teaches rare circumstances, Jaillon et al. (Nature, Vol. 451, 2008, pages 359-363) teach that most eukaryotic genes are

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interrupted by non-coding introns that must be accurately removed from pre-messenger RNAs to produce translatable mRNAs and that the mechanisms specifying the correct sites remain poorly understood. Jaillon et al. teach that short introns recognized by the intron definition mechanism cannot be efficiently predicted solely on the basis of sequence motifs. Jaillon et al. teach that the intrinsic efficiency of splicing varies widely among introns (see abstract).

It is noted that introns can be inserted into genes to control the expression of the gene, as evidenced by the state of the art; (including Gattermann; and Yoshimatsu and Nagawa et al., as cited by applicant). However, none of the references are enabling for a broad method of inserting any intron into any position of any sequence encoding any gene product wherein the resultant eukaryotic sequence would express more than one copy of a sequence. None of these references enable the instant genus of predictable splicing of any intron inserted at any position within a sequence encoding any polymerase or gene product.

Again, the issue is not whether it was known in the art how to insert introns, but rather how to insert introns in a predictable fashion in accordance with the breadth of the instant claims and have the desired outcome specific to eukaryotic and prokaryotic cells with regards to any polymerase, as recited in the instant claims. Balvay et al. is simply an example that secondary structure is one complexity when considering splicing mechanisms. The instant claims embrace insertion into locations such as those taught by Balvay.



Applicant argues that Balvay is contrary to published material that explicitly states that such a procedure is predictable and essentially problem-free. However, applicant has not pointed to any publication or teaching in the art that teaches that the instant claim scope is predictable or problem-free to support this statement.

In particular, it is demonstrated that the complex secondary structures of nucleic acids are responsible for their intron excision activity, and furthermore, that predicting the ability of the cellular splicing machinery to splice out precise intervening sequences from disrupted sequences with variable secondary structures such that native activity is restored is considered unpredictable, because the splicing machinery is sensitive to the presence or absence of such structures.

Applicant relies on Lewin for teachings regarding experiments of splicing out a hybrid intron and teachings that splicing sites are generic, meaning that they do not have specificity for individual RNA precursors and the RNA precursors do not convey specific information (such as secondary structure) that is needed for splicing. The teachings of Lewin et al. do not diminish the unpredictability of the intron splicing mechanism when a non-native intron is inserted into a sequence having secondary structure. Simply because splice sites are generic to different sequences that do not “convey” secondary structure that is needed for splicing does not mean that the mechanism does not encounter problems of unpredictability as taught by Balvay et al.

Furthermore, the replacement of even a few nucleotides on an mRNA can abolish all activity of the translated protein. It is maintained that neither the specification nor the prior art arms one of skill with the information necessary to engineer sequences

into nucleic acid constructs that will be reliably spliced out to result in a protein with native activity restored.

In the absence of sufficient guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Applicant argues that there is no need for *de novo* determination of intervening sequences because the art teaches introns that can be fully spliced out. The examiner is not arguing that there is not evidence of intron splicing in the art, but rather lack of evidence of predictable splicing and expression in eukaryotic cells commensurate in scope with the instant claims.

MPEP 2164.01

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a)

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The instant specification at page 85, last paragraph, sets forth that it is possible that insertion of a heterologous processing element may not in all cases inactivate a gene when present in an incompatible cell and therefore supports the unpredictability of the instantly claimed breadth.

The specification further sets forth that introns from eukaryotic genes have been introduced into prokaryotic genes with the result of an altered protein.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 245, 247-255, 262, 265, 270, and 271 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 11/929,055. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of application '055 are directed to a construct comprising a nucleic acid encoding a polymerase and a non-native intron sequence wherein the polymerase is incapable of being expressed in a prokaryotic cell and is capable of producing more than one copy of a nucleic acid in a eukaryotic cell, which are each elements of the instant claims. Furthermore, each of the additional elements of the instant claims are embodiments of the '055 claims, as supported by the specification of application '055.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant sets forth that this rejection will be addressed once there is indication of allowable subject matter.

***New Objections/Rejections***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 255 and 265 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz et al. (Gene, 127, 1993, pages 233-236).

Schwartz et al. teaches introduction of an intron from a hamster gene into a neo gene such that splicing of the neo gene mRNA results in the synthesis of active aminoglycoside phosphotransferase. The unspliced construct is inactive in E. coli, but confers resistance to G418 when transfected into mouse and hamster cells. Schwartz et al. is evidence that it was known in the art to utilize the insertion of introns to control expression of a gene product in prokaryotic versus eukaryotic cells.

Therefore, the claims are anticipated by Schwartz et al.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 245, 247-255, 262, 265, 270, and 271 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. (Gene, 127, 1993, pages 233-236),

in view of Mount (Nucleic Acids Research, Vol. 10, No. 2, 1982, pages 459-472), and Deuschle et al. (Proc. Natl. Acad. Sci., Cell Biology, Vol. 86, 1989, pages 5400-5404).

The Schwartz et al. and Mount references are of record.

Schwartz et al. teaches introduction of an intron from a hamster gene into a neo gene such that splicing of the neo gene mRNA results in the synthesis of active aminoglycoside phosphotransferase. The unspliced construct is inactive in *E. coli*, but confers resistance to G418 when transfected into mouse and hamster cells. Schwartz et al. is evidence that it was known in the art to utilize the insertion of introns to control expression of a gene product in prokaryotic versus eukaryotic cells.

Schwartz et al. do not teach the system specific to a polymerase, do not teach (C/A)AG sites.

Mount teaches splice junction sequences such as (C/A)AG and teach that the sequences have a possible role as signals for processing.

Deuschle et al. teach the development of a highly regulated expression system in mammalian cells in which transcription of a foreign gene is mediated by the bacteriophage T3 RNA polymerase under the control of the *E. coli* lac repressor. Deuschle et al. teach that a specific transcription activity can be regulated over a range of several orders of magnitude in higher eukaryotic cells.

The concept of utilizing the insertion of introns to control expression of a gene product in prokaryotic versus eukaryotic cells is taught by Schwartz et al. Although Schwartz is silent as to (C/A)AG sites, it would have been obvious and well within the technical grasp of a skilled artisan to insert the intron next to such a site given that these

sequences were known in the art to be present at splice junction sites, which are crucial sites to the splicing of such intron sequences.

It would have been obvious to insert the intron into a sequence encoding a polymerase given that it was known in the art that bacteriophage T3 RNA polymerases are crucial in gene expression systems that regulate genes in eukaryotic cells. One would have been motivated to do so in order to attempt to control the expression of the polymerase in prokaryotic/eukaryotic cells since Schwartz et al. teaches that introns can be inserted to control differential expression.

Primer selection as well as insertion of the intron at a known splice site sequence is considered within the realm of routine optimization, as these are elements that were routinely utilized in the art in gene expression control systems.

One would reasonably expect for insertion of an intron of Schwartz et al. at a known splice site or insertion into a sequence encoding for bacteriophage T3 RNA polymerases to result in expression in a eukaryotic cell without expression in a prokaryotic cell.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571) 272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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